

Genéricos

CON



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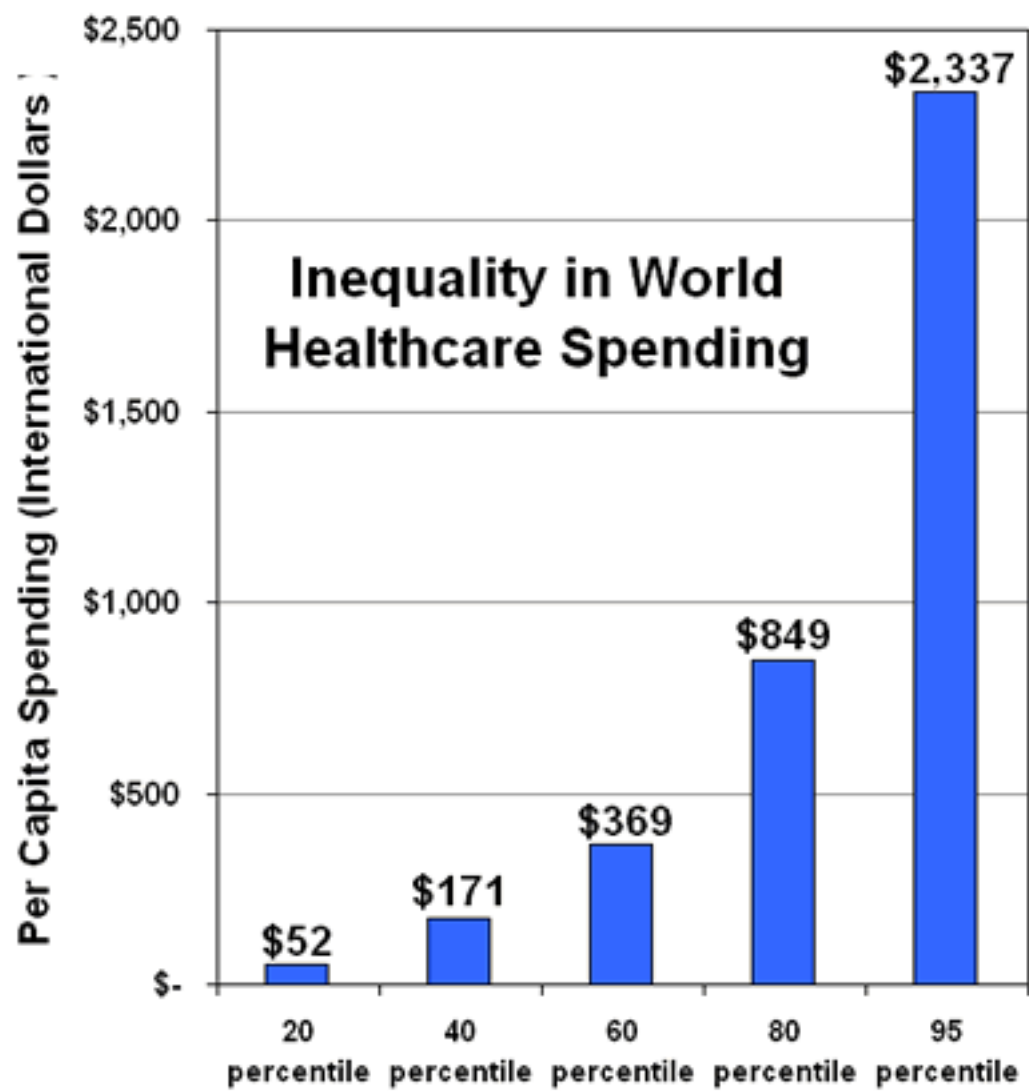
**Advisory Committee Recommendations on
Generic Substitution of
Immunosuppressive Drugs**

Dr. Teun van Gelder

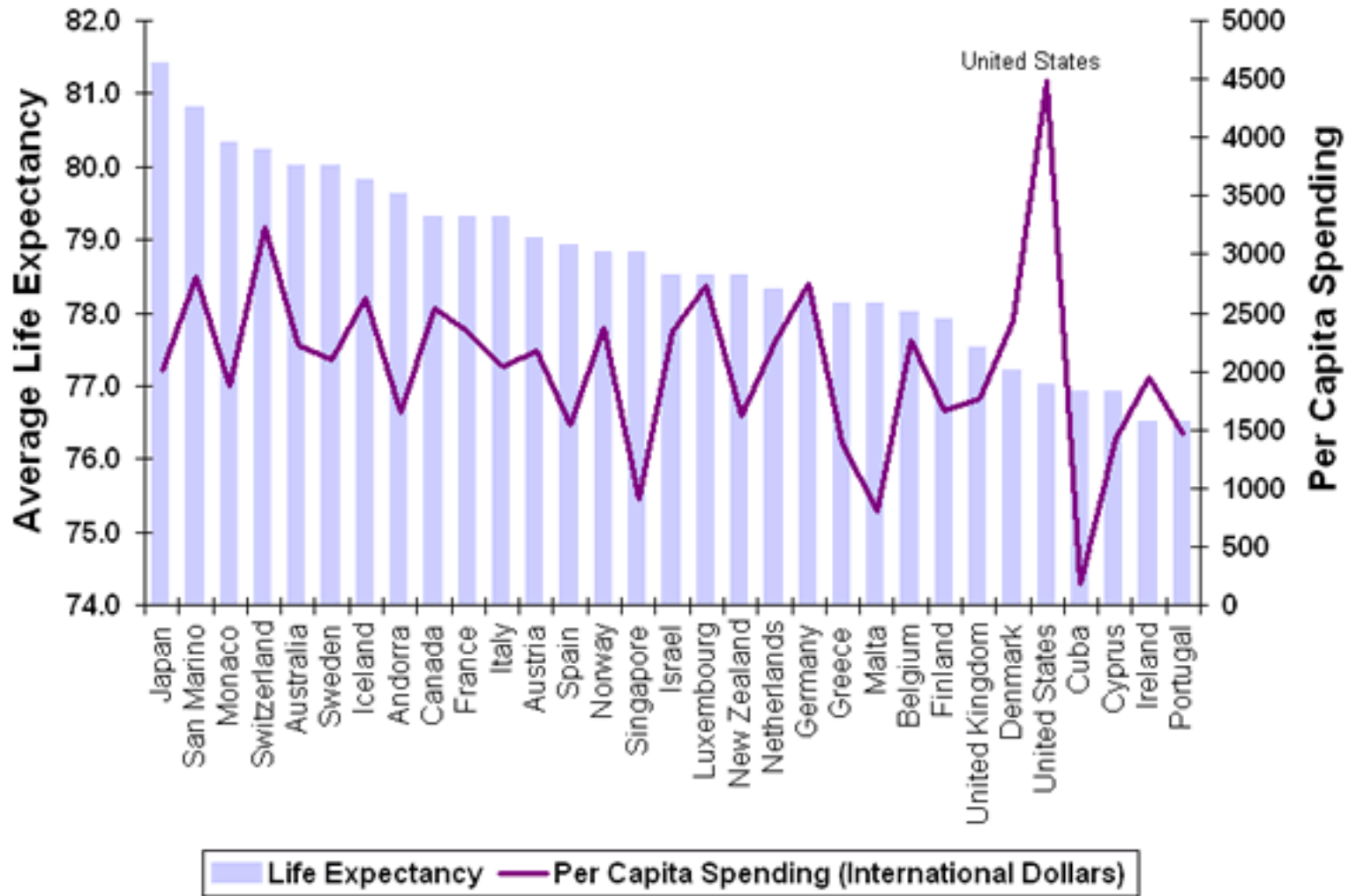
**(on behalf of the ESOT Advisory
Committee on Generic Substitution)**

(July 7 2011)

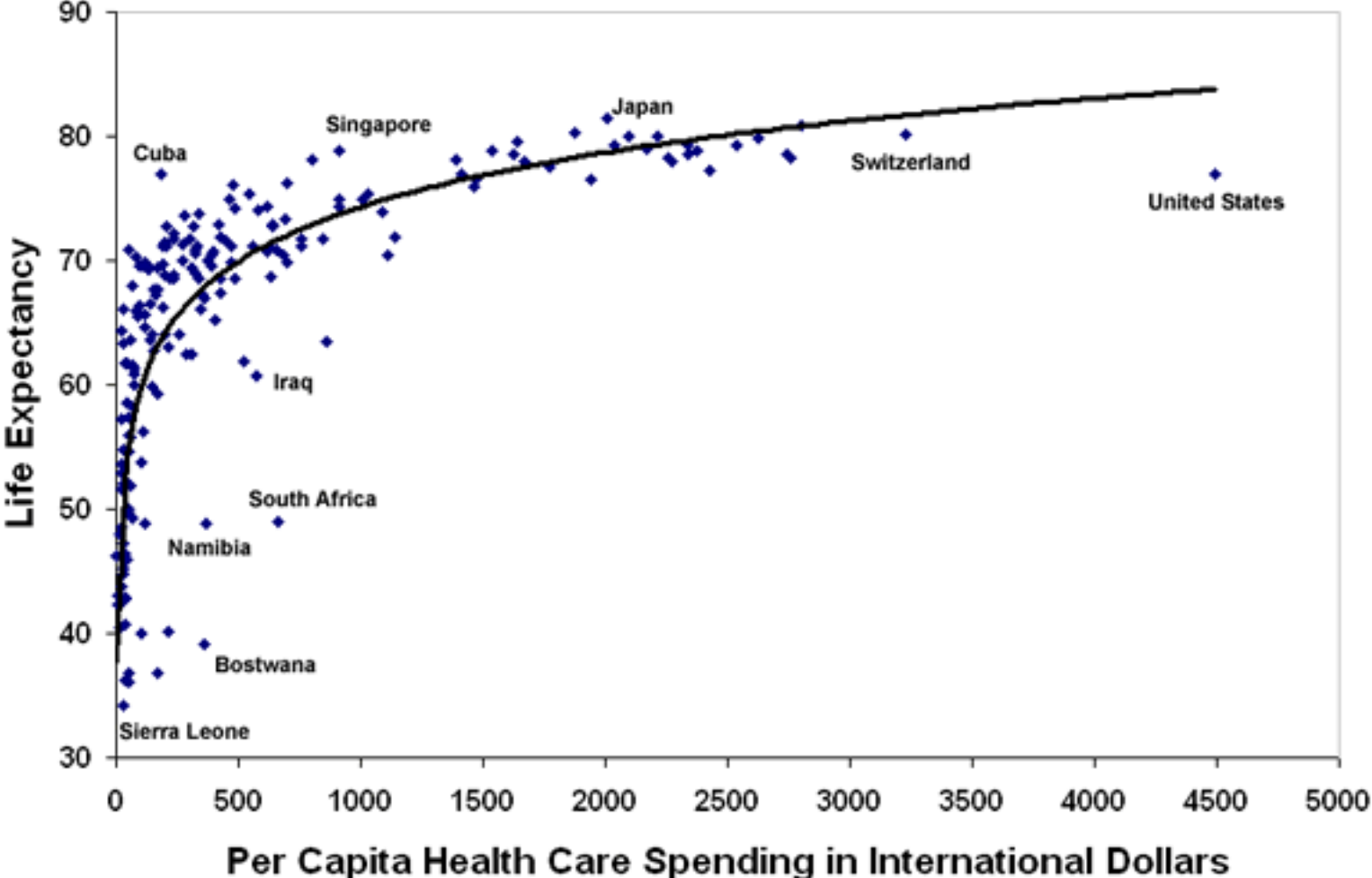




The Cost of a Long Life



Life Expectancy vs. Spending



7.4.1 Expenditure on pharmaceuticals per capita and as a share of GDP, 2009 (or nearest year)

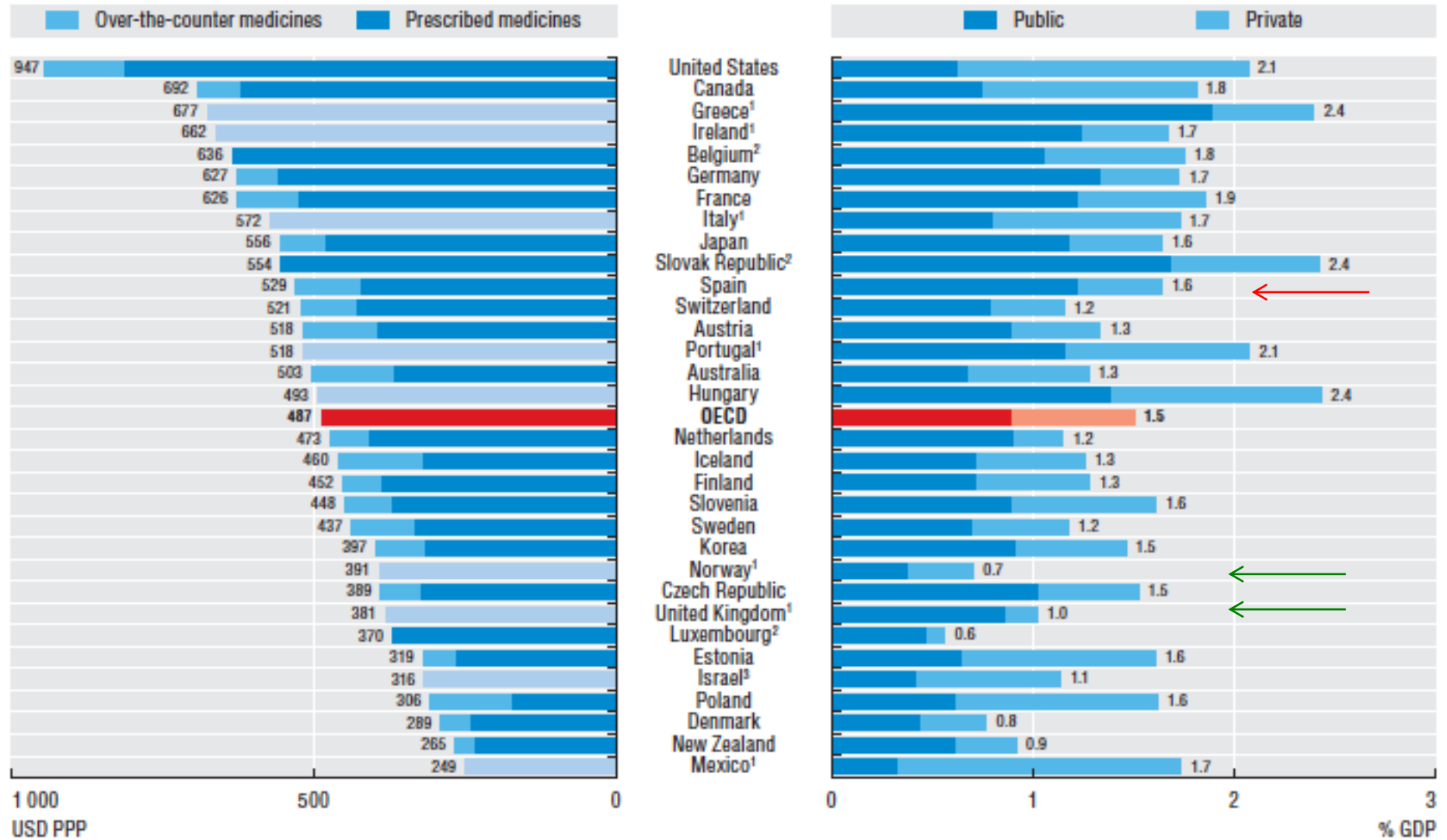
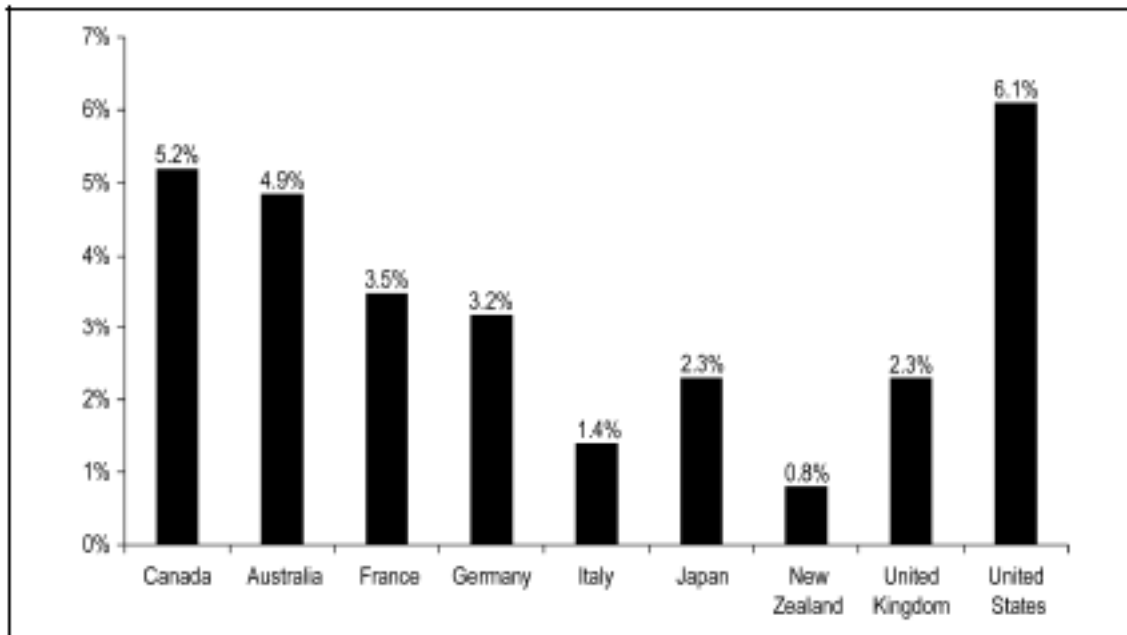


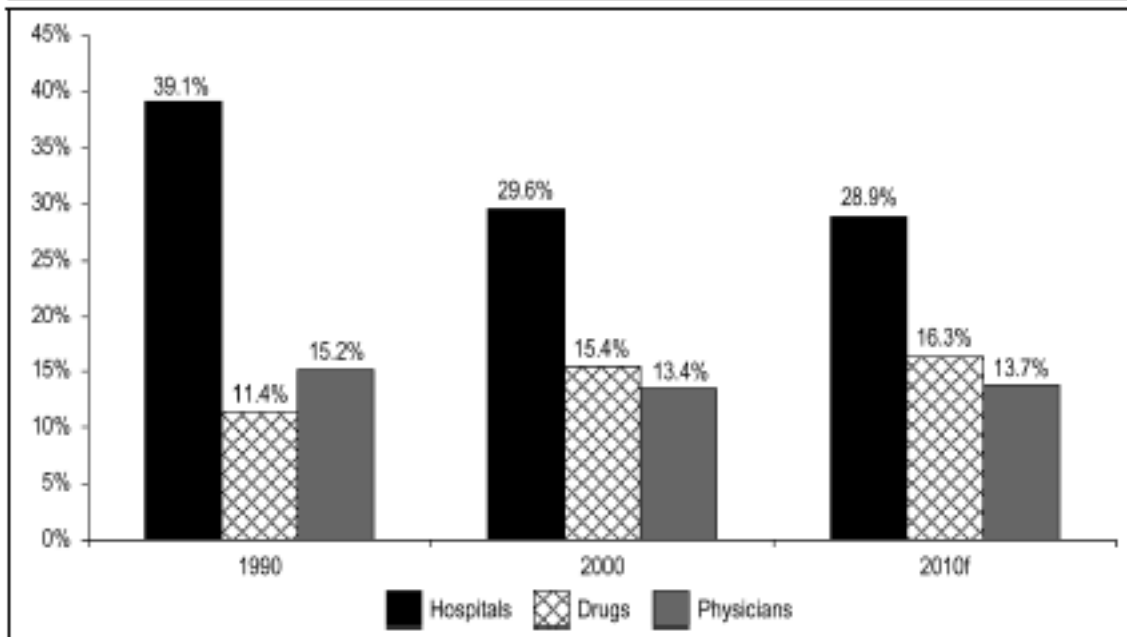
Figure 3: Average Annual Growth in per Capita Drug Spending, Selected Countries, 1997 to 2007



Source

Organisation for Economic Co-operation and Development and IRDES, *OECD Health Data 2010* (Paris, France: OECD and IRDES, October 2010).

Figure 1: Percentage Share of Total Health Spending, by Selected Category, Canada, 1990 to 2010



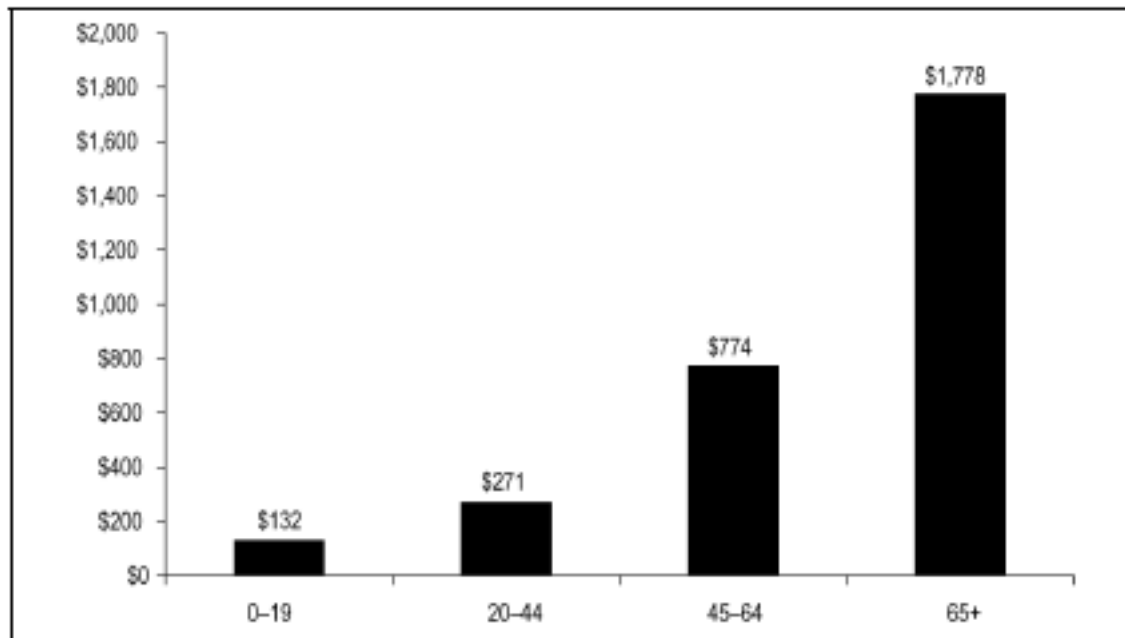
Note

f: forecast.

Source

National Health Expenditure Database, 2011, Canadian Institute for Health Information.

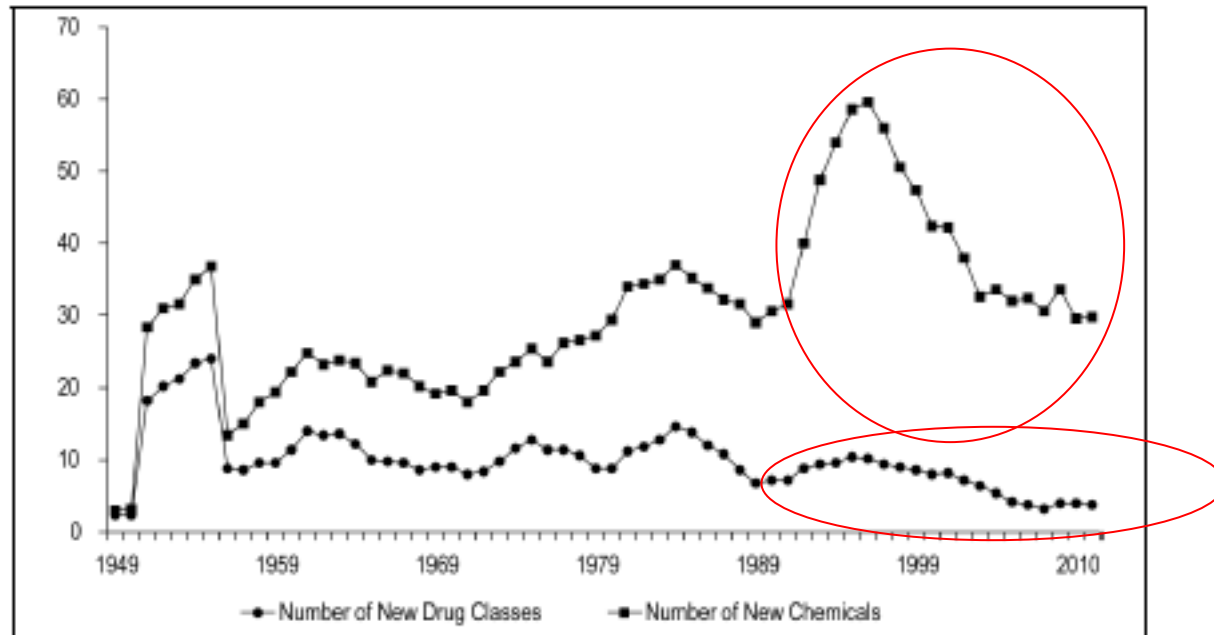
Figure 5: Per Capita Retail Drug Expenditure by Age Group, Canada, 2007



Source

S. Morgan et al., *The Canadian Rx Atlas, 2nd Edition* (Vancouver, B.C.: Centre for Health Services and Policy Research, University of British Columbia, 2008).

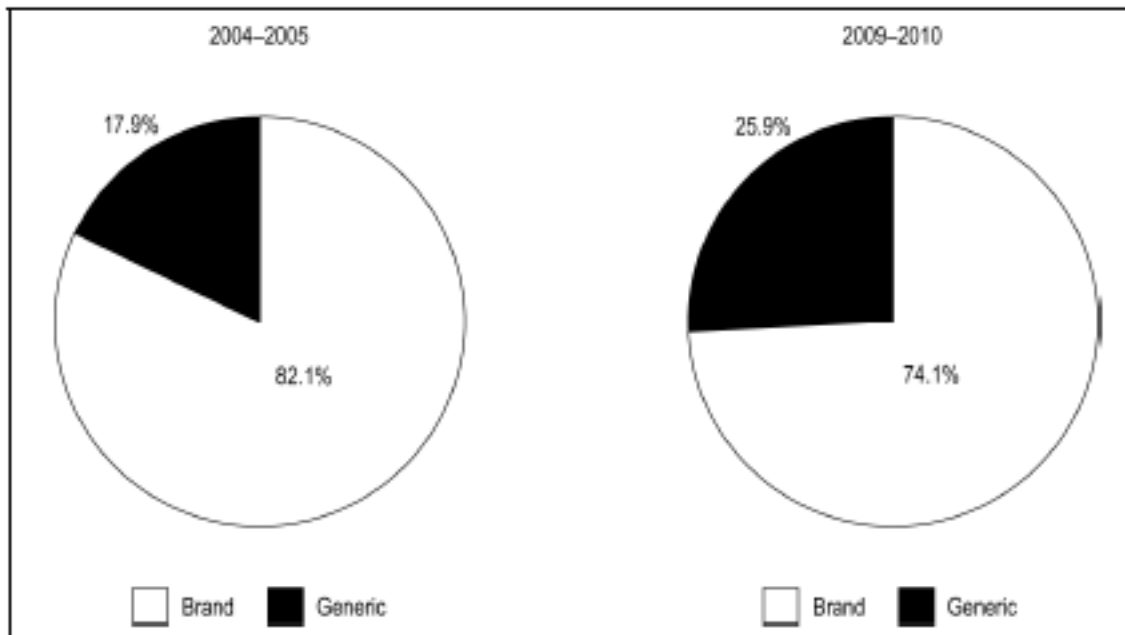
Figure 8: Five-Year Averages of New Chemicals and New Drug Classes Approved for Sale in Canada, 1949 to 2010



Sources

National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information; Drug Product Database, Health Canada.

Figure 6: Percentage Share of Wholesale Drug Purchases (Drug Stores and Hospitals), Brand Name and Generic, 2004–2005 and 2009–2010

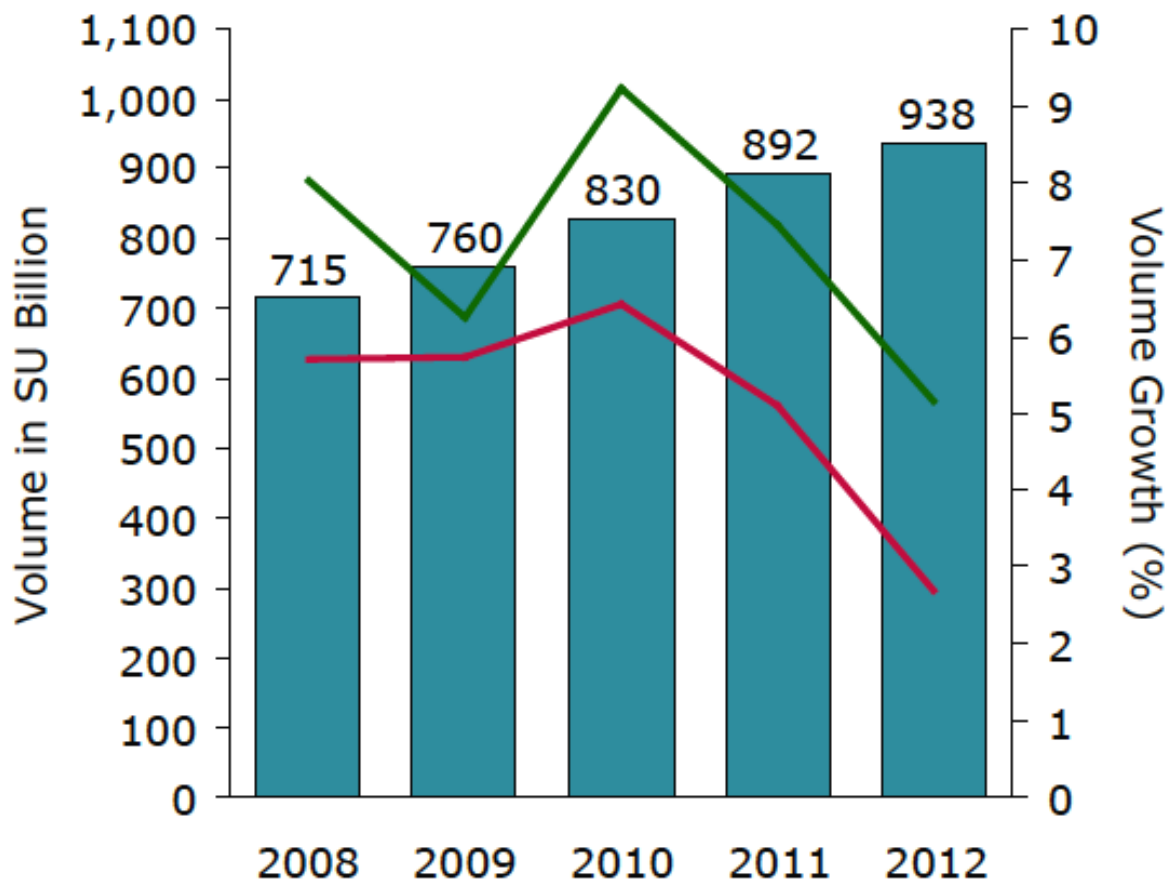


Source
Canadian Drug Store and Hospital Purchases Audit, 2010, IMS Brogan.



Generics have seen superior growth performance for a number of years

2008-2012: Global Generic Volume Sales



- Growth is driven by government that under high debt and fiscal deficits are pushing for even greater generication
- In Pharmerging countries growth is underpinned by generic growth
- Fewer, smaller small molecules going forward

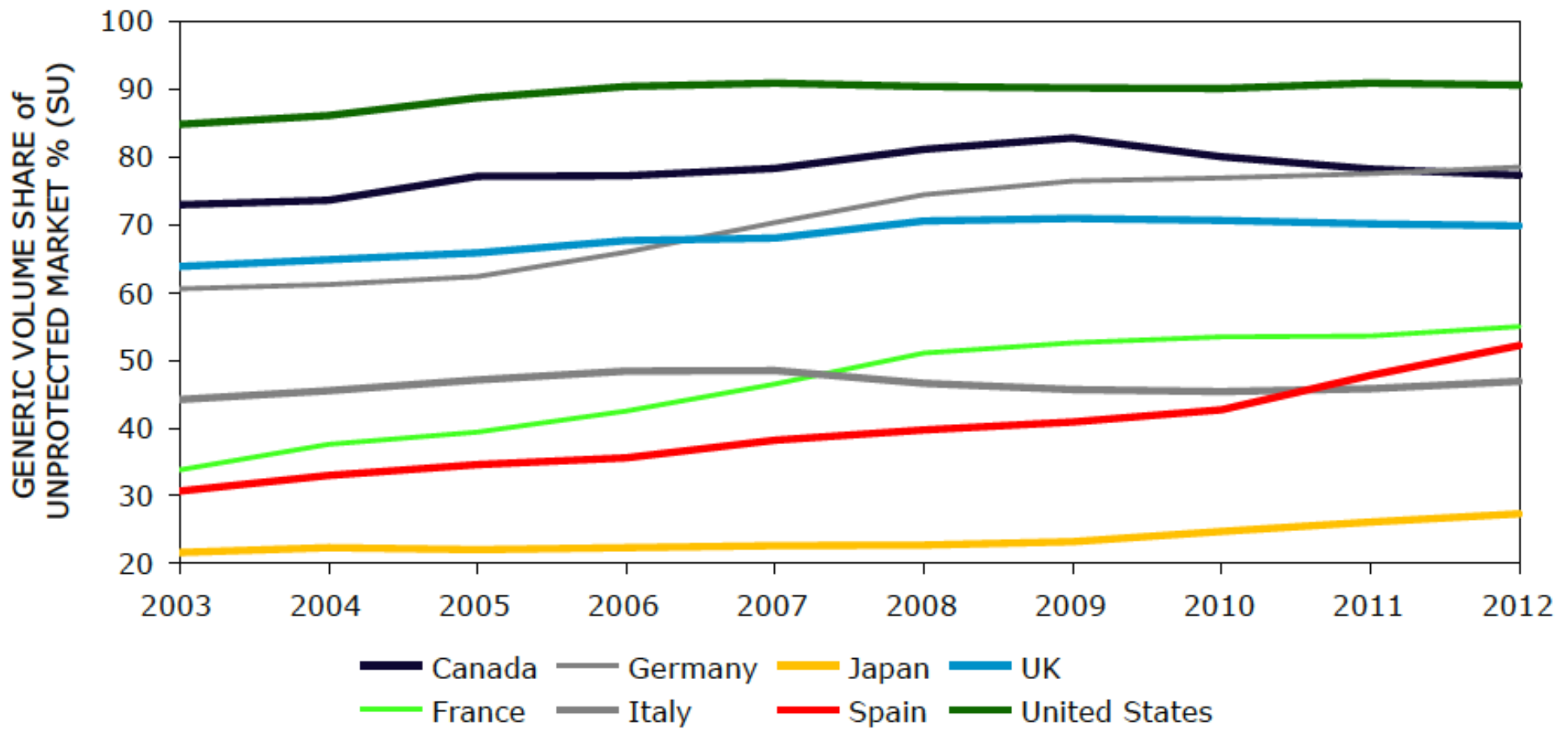
Category	5 yr CAGR
Pharma	5.0%
Generics	7.2%

— Generic Volume Growth — Pharma growth ■ Generic Volume

Source: IMS Health, MIDAS, MAT Sept 2012, Rx only. Market Segmentation + LIC countries

Historically generic penetration moves slowly even in large markets: recently Spain has accelerated

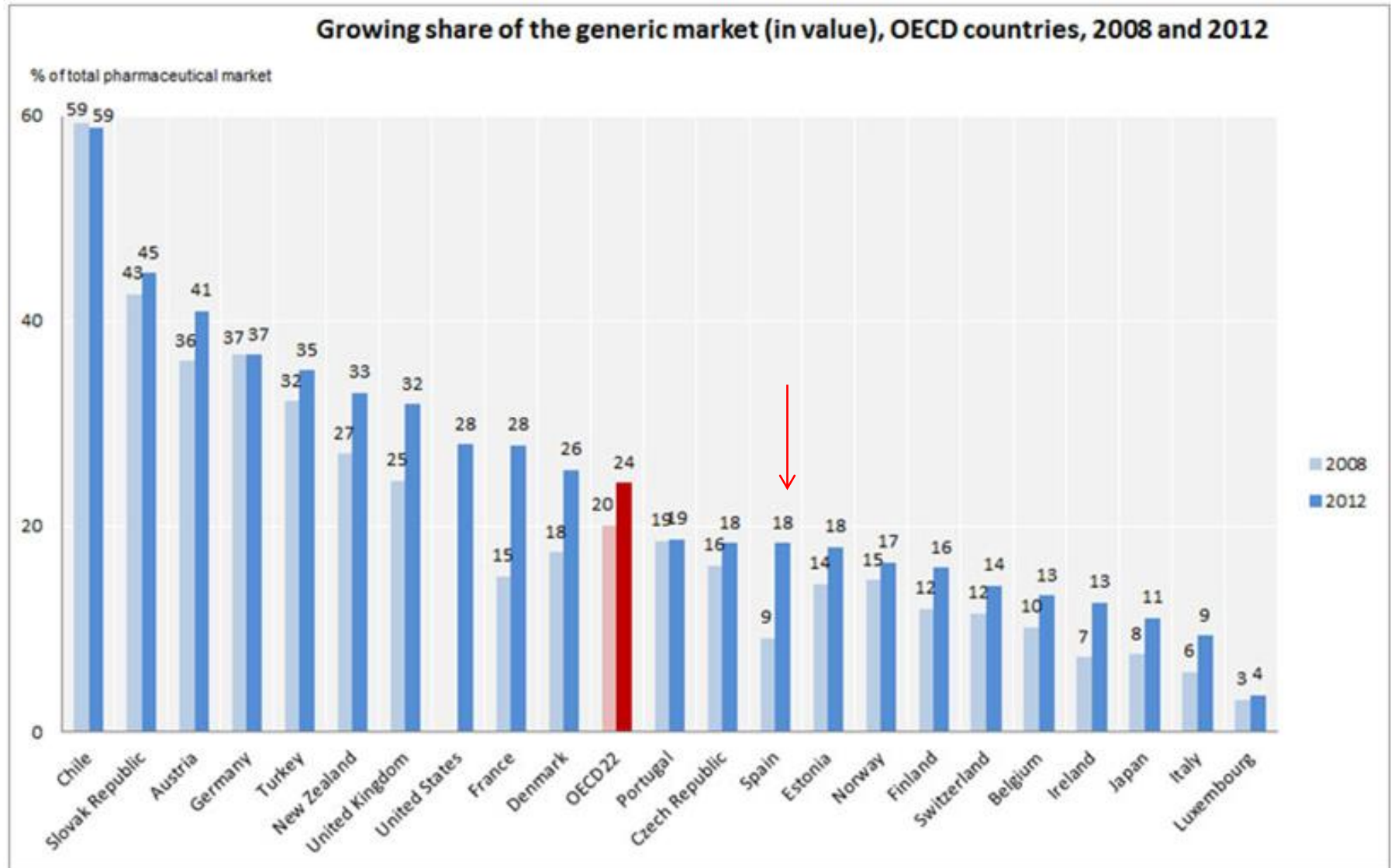
2003-2012: Generic volume penetration dynamics in the top 8 markets



Source: IMS MIDAS Sep 2012 Ethical Total Market based on SU.

PRESS RELEASES

Spain is the country in the OECD with the fastest generic penetration
Publication of the 110th issue of Farmaindustria's Monthly Economic Bulletin
(11-09-2014)



Factors that have been shown to drive generic utilisation and factors that inhibit generic utilisation

Drivers



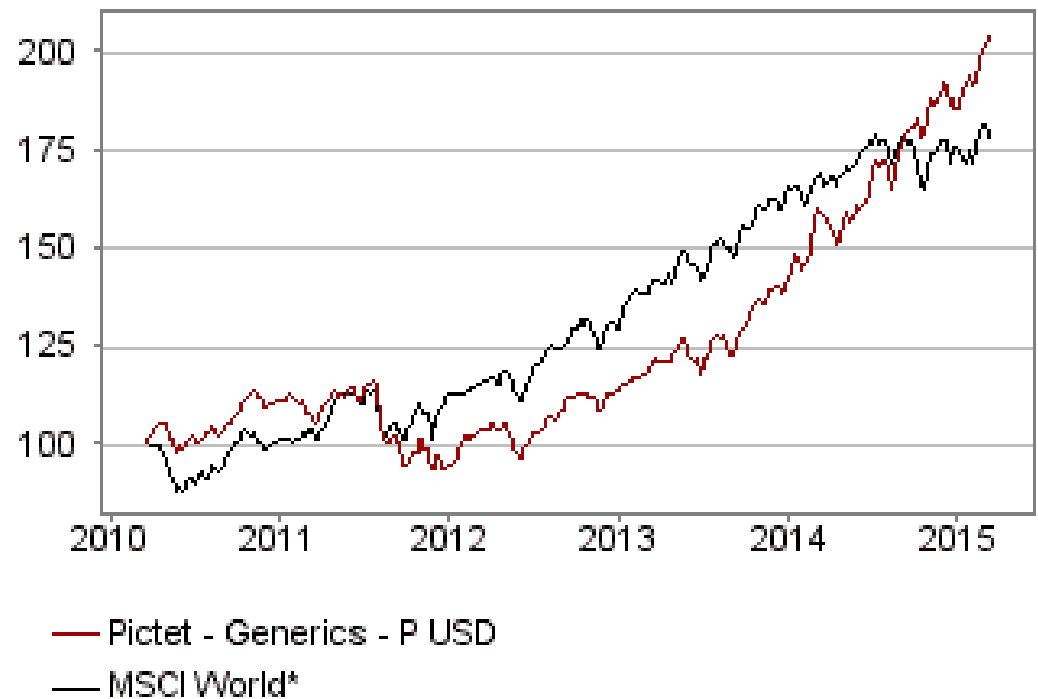
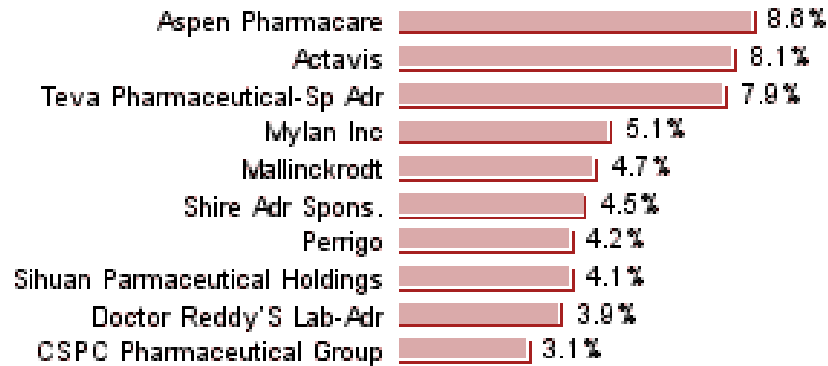
- Mandatory INN prescribing
- Generic first dispensing and prescribing
- Large price differential between generic and originator
- Reimbursement levels
- Patient Co-payments
- Incentives for dispensing/prescribing generics



Constraints

- Cultural resistance from doctors
- Lack of incentives for pharmacists to dispense
- Lack of margin for wholesalers to distribute
- Preference for brands in certain markets
- Across the board price cuts

Funds on generics



Cumulative performance index: 77%



Maintenance immunosuppressive therapy and generic cyclosporine A use in adult renal transplantation: a single center analysis

Danielle A. Diarra¹, Markus Riegersperger¹, Marcus D. Säemann¹ and Gere Sunder-Plassmann¹

¹Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria

The Role of Generics in Kidney Transplant: Mycophenolate Mofetil 500 Versus Mycophenolate: 2-Year Results

Taieb Ben Abdallah,¹ Mondher Ounissi,² Mejda Cherif,¹ Imed Helal,² Cyrine Karoui,¹ Sonia Mhibik,¹ Med Mongi Bacha,¹ Ezzeddine Abderrahim,² Adel Kheder²

© Ann Transplant, 2011; 16(2): 59-62

Original Paper

American Journal of Transplantation 2011; 11: 1861–1867
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Transplantation and the American Society of Transplant Surgeons
doi: 10.1111/j.1600-6143.2011.03615.x

The Impact of Conversion From Prograf to Generic Tacrolimus in Liver and Kidney Transplant Recipients With Stable Graft Function

J. D. Momper^a, T. A. Ridenour^b,
K. S. Schonder^c, R. Shapiro^d, A. Humar^d
and R. Venkataramanan^{a,e,*}

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Generic formulation of Cyclosporine A, Equoral[®], in *de novo* kidney transplant recipients: Five-year follow-up

Mariusz Niemczyk^{ABCEFG}, Leszek Pączek^{ADFG}

Department of Immunology, Transplant Medicine, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

Immunosuppressive regimens containing generic mycophenolate mofetil (Myfenax) in *de novo* renal transplant recipients – preliminary results of 6-month observation

Bolesław Rutkowski, Beata Bzoma, Alicja Dębska-Ślizień, Andrzej Chamienia

Ann Transplant 2011; 16(4): 74-80

Immunosuppression With Generic Tacrolimus and Mycophenolate Mofetil in Renal Transplant Recipients: Preliminary Report in Chile

H. Müller, S. Solari, C. Zuñiga, C. Pedreros, J. Troncoso, C. Morente, R. Ovalle, P. Acosta, T. Chavez, E. Albornoz

DOI: <http://dx.doi.org/10.1016/j.transproceed.2008.02.056>

Can Generics Be Trusted?

Anecdotal reports question the safety of generic immunosuppressants

Among themselves, physicians have shared safety concerns after patients switched to generic versions of the mainstay immunosuppressants Prograf (tacrolimus) and/or CellCept (mycophenolate mofetil). But so far, such concerns are based on anecdotes—not published studies. “The pattern we’ve seen is that some previously stable patients who’ve been switched to a generic have had late rejections, and that raises our antenna,” says John Friedewald, MD, a nephrologist at Northwestern Memorial Hospital in Chicago.

At the Cleveland Clinic, John Fung, MD, PhD, chairman of the Department of General Surgery, notes that one of their stable patients converted to a generic because his insurance company required him to, and he ended up having about a 30% reduction in tacrolimus trough level. After the transplant team biopsied the organ and talked with the insurance company, the third-party payer rescinded the decision and agreed to cover Prograf.

If these stories sound familiar, don’t count on them to sway the Food and Drug Administration (FDA) to take a closer look at generics. The FDA approved the first generic version of tacrolimus in August and several generic versions of mycophenolate mofetil this past year. However, the agency will need hard data before it will change its generic approval process.

FDA Need Scientific Evidence

Crystal Rice from the FDA’s Center for Drug Evaluation and Research says the agency would like to see actual data—not anecdotes from random patients—showing that generics are not performing the way they should. “If we see scientific evidence that there is a problem with a generic, we will take action,” she says.

letters from the American Society of Transplantation [AST] and the American Society of Transplant Surgeons [ASTS]) asked for further studies. They requested that in “orally administered immunosuppressants used in the transplant population and characterized by a narrow therapeutic index, such as tacrolimus, bioequivalence studies in healthy subjects be supplemented by studies performed in the transplant population.”

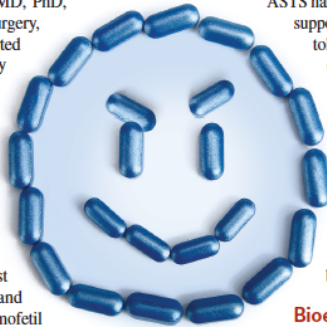
Nearly two years later, in August 2009, the FDA finally responded in a letter to Astellas that said, in part, “We note that

ASTS has provided no new scientific or clinical data to support their comments.” Additionally, the FDA

told Astellas that they “do not agree that bioequivalence studies in transplant patients should be required for the approval of ANDAs [abbreviated new drug applications] for tacrolimus drug products. . . . With regard to tacrolimus, there is insufficient scientific evidence to suggest that the use of specific patient population(s) in bioequivalence studies would detect differences in formulation that might have clinical significance and that would not be detected by bioequivalence in healthy subjects.”

Bioequivalence Can Vary by 40%

Rice says that test and reference drugs are considered bioequivalent if both provide the same rate and extent of absorption as determined by the bioequivalence measure C_{max}, which is the peak plasma drug concentration following a single dose, and the AUC, which is the area under the drug plasma concentration versus sampling time curve following a single dose. “Two drugs are deemed bioequivalent if the 90% confidence intervals of the geometric mean C_{max} and AUC test/reference ratios fall within the limits of 80% to 125%,” she adds.



Transplantation. 2012 Apr 15;93(7):657-65. doi: 10.1097/TP.0b013e3182445e9d.

Generic immunosuppression in solid organ transplantation: a Canadian perspective.

Harrison JJ1, Schiff JR, Coursol CJ, Daley CJ, Dipchand AI, Heywood NM, Keough-Ryan TM, Keown PA, Levy GA, Lien DC, Wichart JR, Cantarovich M.

Immunosuppression, Generic Drugs and the FDA

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even more concerning. In this study, the follow-up period was short and, as carefully pointed out, “accompanied by vigilant therapeutic drug monitoring mitigating the risk of rejection, acute or chronic.”

There are currently four approved generic tacrolimus prod-

Letter to the Editor

doi: 10.1111/j.1600-6143.2011.03875.x

Immunosuppression, Generic Drugs and the FDA

To the Editor:

We respectfully disagree with some points voiced in Dr. Klintmalm’s editorial regarding generic immunosuppression (1).

tered by the associated cost of increased laboratory monitoring.

We acknowledge that further research is necessary to determine the pharmacoeconomic impact of generic im-

J Nephrol. 2004 Nov-Dec;17 Suppl 8:S20-4. Generic cyclosporine: a word of caution. Ponticelli C1.

Therapeutic index

- **Therapeutic index**
 - The range between the median effective dose, known as ED50, and the median toxic dose, TD50
- **Narrow therapeutic index (NTI)**
 - A very small range of doses at which a medication provides benefits without causing severe and potentially fatal complications
- **Small molecule immunosuppressants are NTI drugs:**
 - Cyclosporine, tacrolimus, MPA agents, mTORi



- 4.2: Do not use generic compounds that have not been certified by an independent regulatory agency to meet each of the following criteria when compared to the reference compound (*Not Graded*):**
- contains the same active ingredient;
 - is identical in strength, dosage form, and route of administration;
 - has the same use indications;
 - is bioequivalent in appropriate bioavailability studies;
 - meets the same batch requirements for identity, strength, purity and quality;
 - is manufactured under strict standards.
- 4.3: It is important that the patient, and the clinician responsible for the patient's care, be made aware of any change in a prescribed immunosuppressive drug, including a change to a generic drug. (*Not Graded*)**
- 4.4: After switching to a generic medication that is monitored using blood levels, obtain levels and adjust the dose as often as necessary until a stable therapeutic target is achieved. (*Not Graded*)**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 October 2014
EMA/618604/2008 Rev. 10
Committee for Human Medicinal Products (CHMP)

Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party

....., in order to ensure the safety and efficacy of generic tacrolimus products it is necessary to apply tighter bioequivalence acceptance criteria than the conventional 80-125%.

Conclusion: The EWP recommends that the bioequivalence acceptance criteria for tacrolimus should be [90-111%] for AUC and [80-125%] for C_{max} CI_{90} (Westlake interval. Biopharmaceutical statistics for drug development. NY: Marcel Dekker, 1988: 329-52)

Main limitations of bioequivalence studies

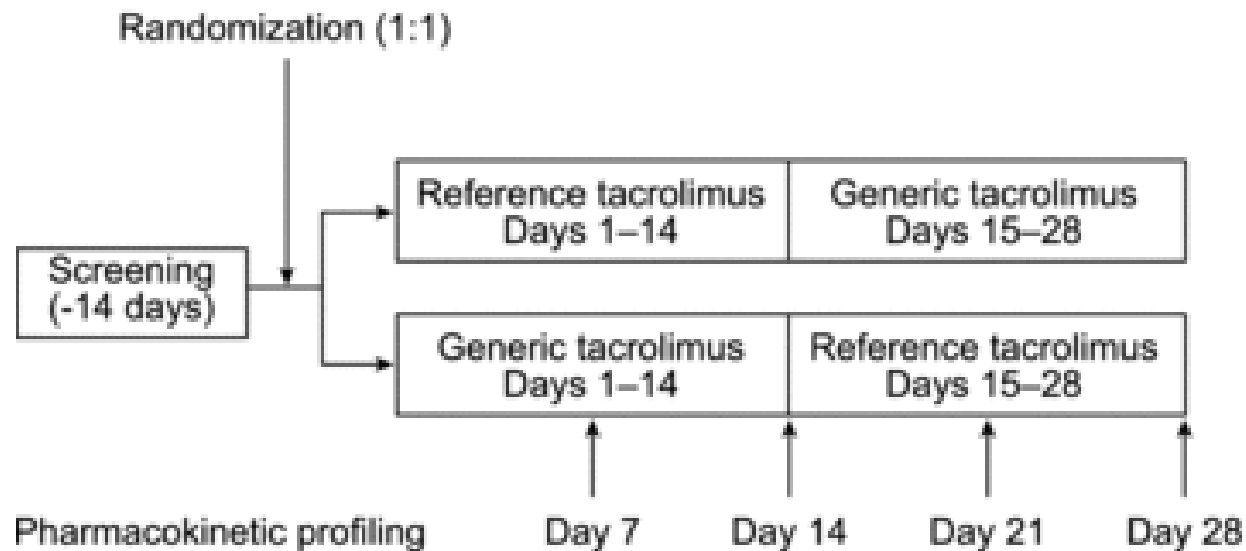
(authorization applications)

- Healthy volunteers (mainly young male adults)
- Single dose crossover studies of innovator drug and generic
- Not in steady state conditions.
- Bioequivalence studies not required among distinct generics formulations:
 - Same active drug
 - Distinct galenic formulations
 - Different bioavailability
- Differences between HV and patients (concomitant medications, polypharmacy, ..)
- Distinct PK parameters for bioequivalence studies and clinical TDM (AUC and C_{\max} vs C_0)

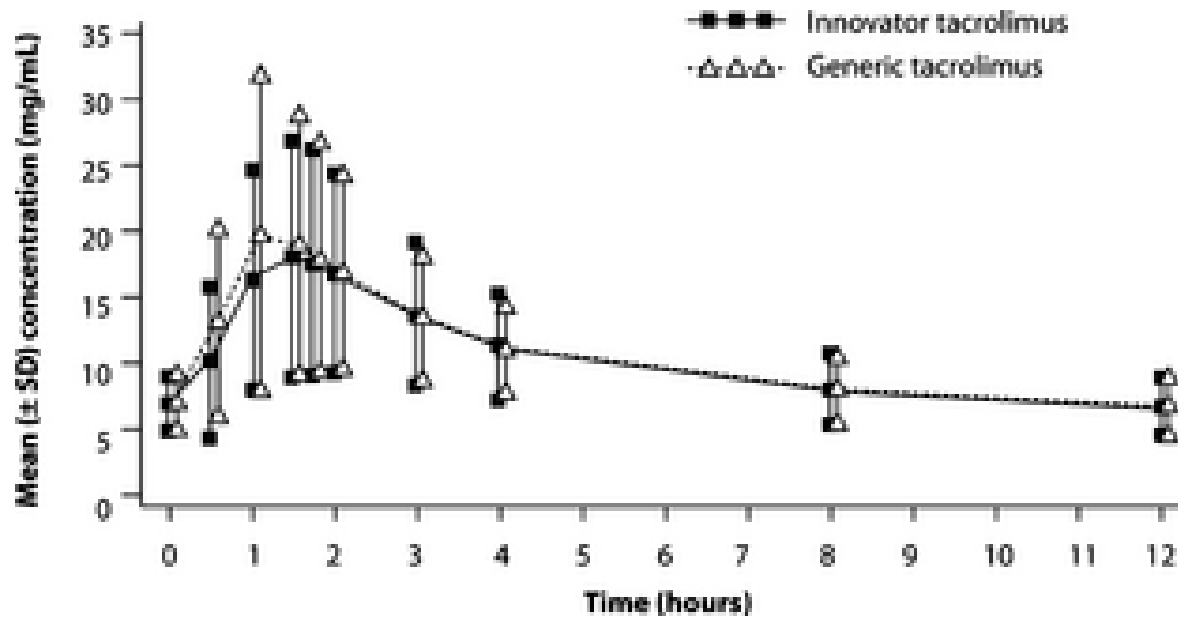
The transplant community is filling the gap.....

beyond regulatory requirements.

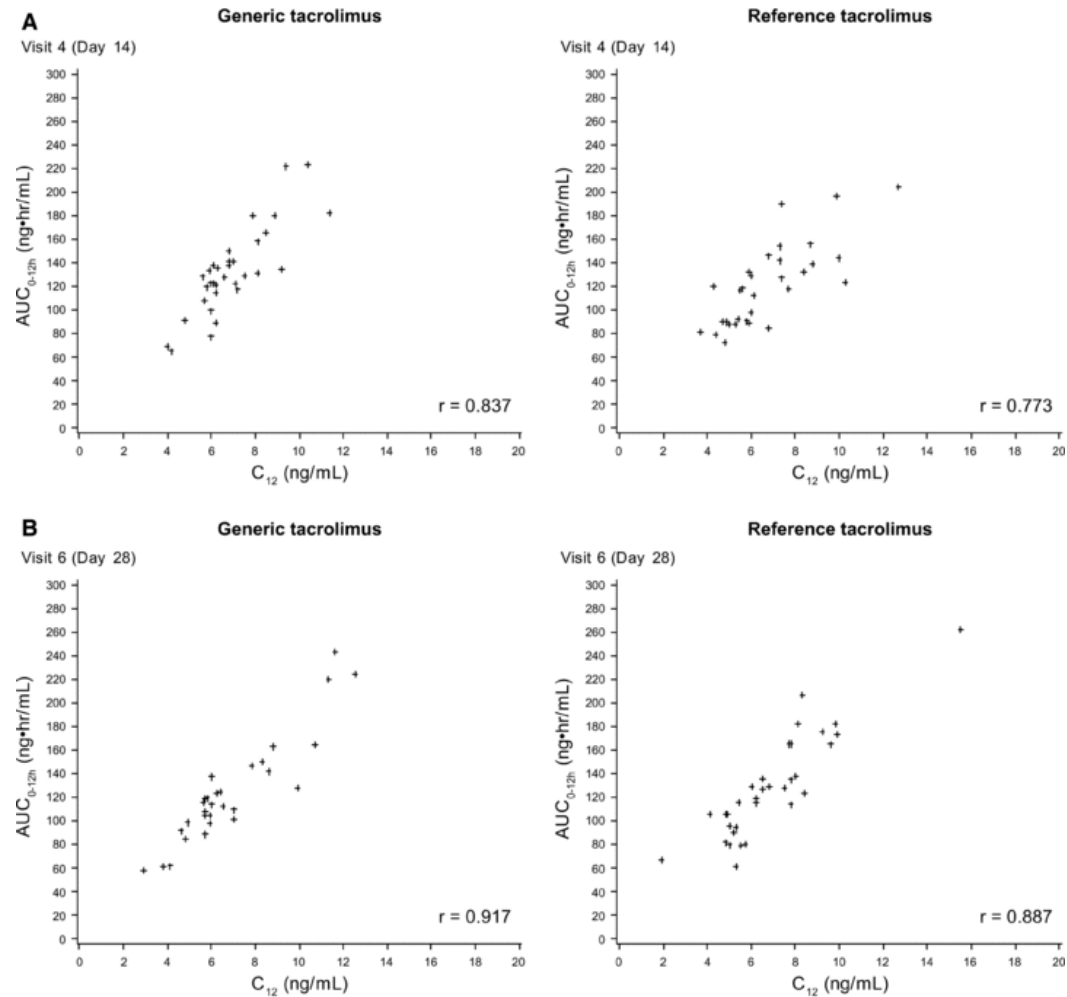
A Randomized Pharmacokinetic Study of Generic Tacrolimus Versus Reference Tacrolimus in Kidney Transplant Recipients



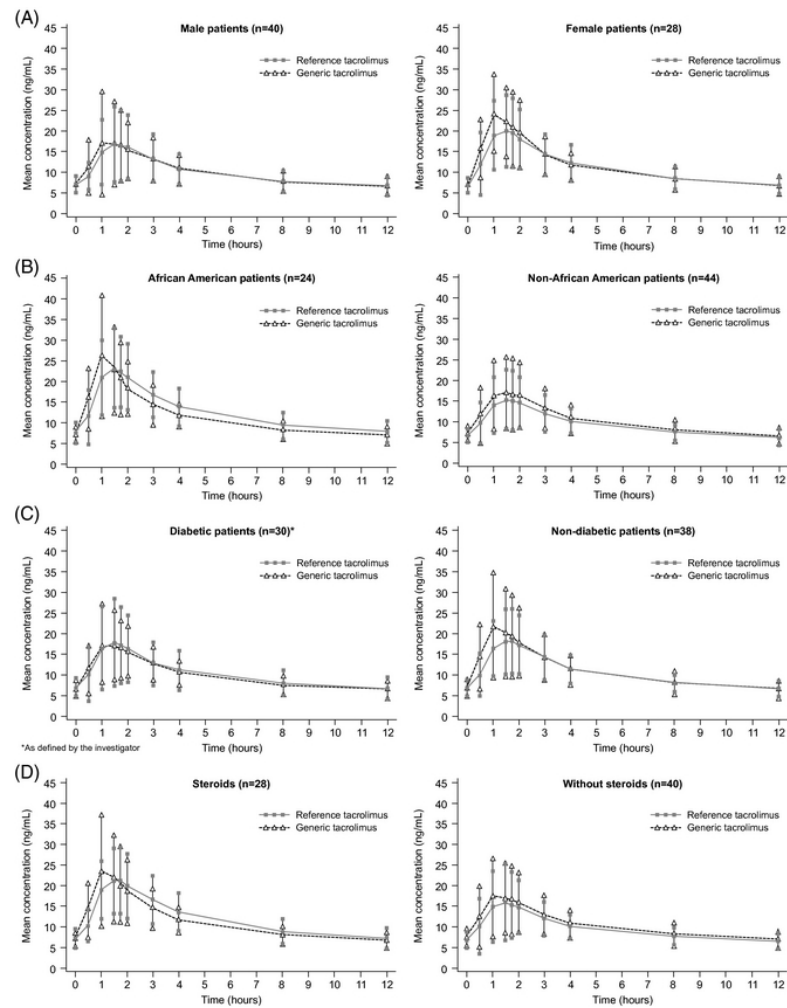
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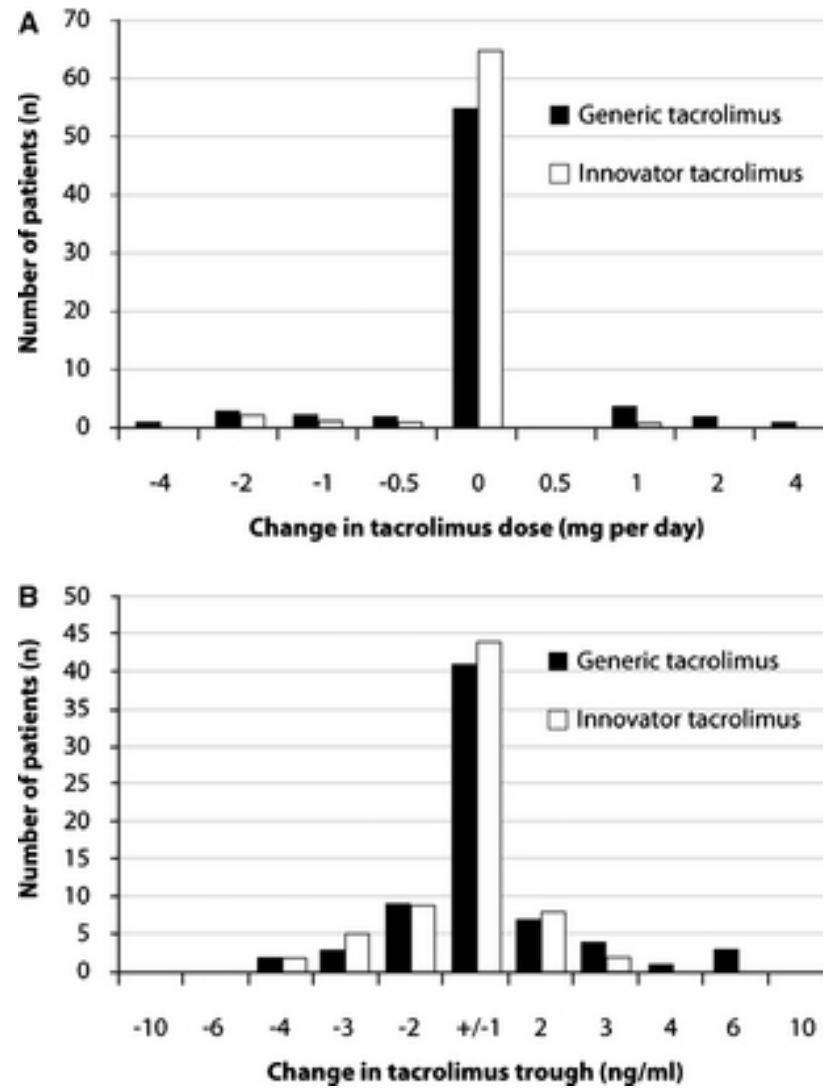
A Randomized Pharmacokinetic Study of Generic Tacrolimus Versus Reference Tacrolimus in Kidney Transplant Recipients



A randomized, crossover pharmacokinetic study comparing generic tacrolimus vs. the reference formulation in subpopulations of kidney transplant patients



Generic tacrolimus in solid organ transplantation Changes in tacrolimus doses and levels



Bioequivalence between generic tacrolimus products marketed in Spain by adjusted indirect comparison

Table 2 Ninety percent confidence interval for C_{max} and AUC of tacrolimus in the bioequivalence studies submitted for marketing approval

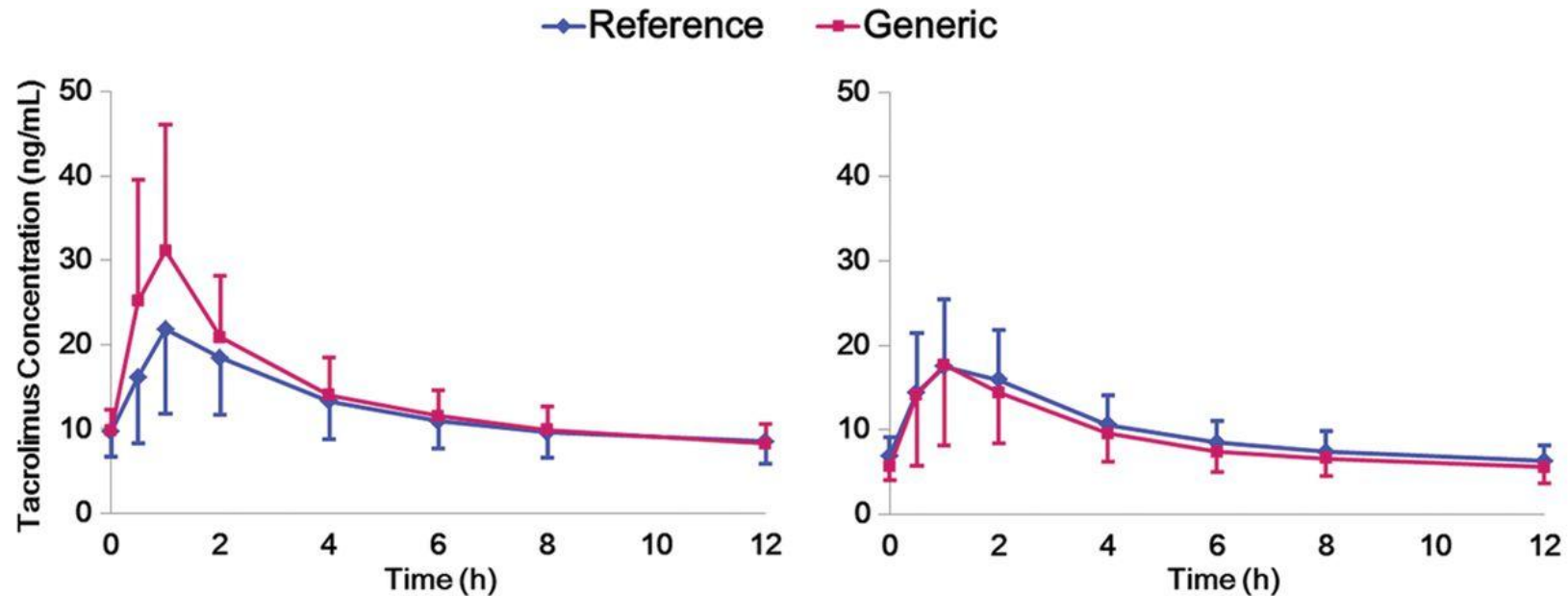
	PharOS		Sandoz		Intas	
	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC
5 mg	105.56–117.93	93.06–104.74	91.69–111.46	99.24–110.89	–	–
1 mg			94.26–111.42	101.12–119.01	103.0–120.8	91.51–105.9
0.5 mg						

However,

- Bioequivalence only required for each generic to the innovator drug and not among them.
- Two generic formulations may not be bioequivalent between them
 - Generic A: CI_{90} : 80-100%
 - Generic B: CI_{90} : 105-125%

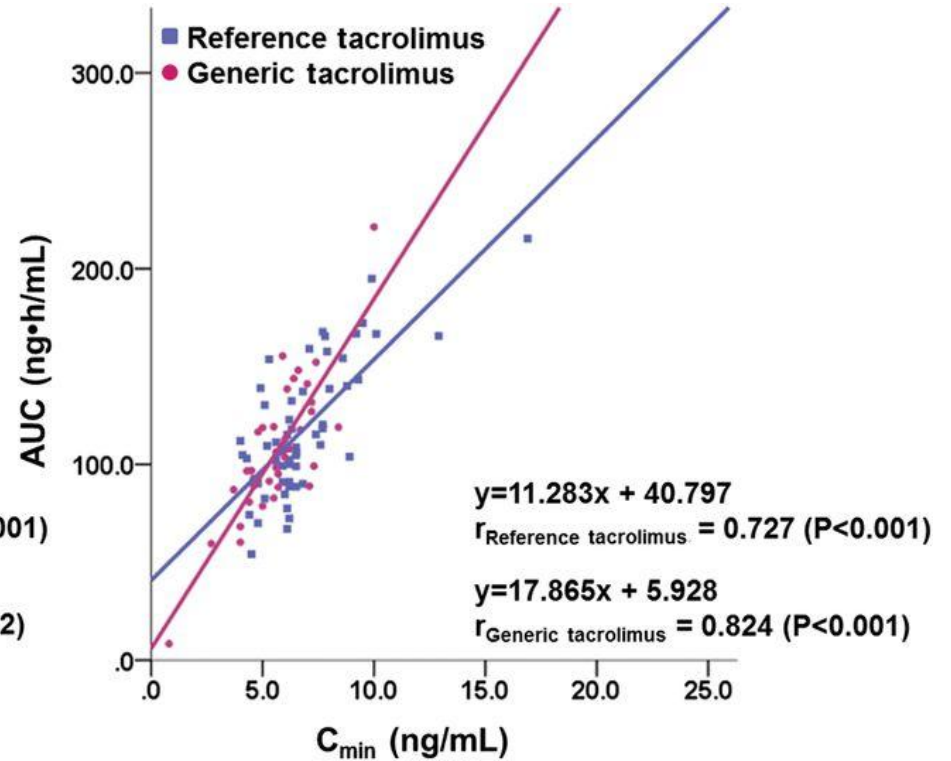
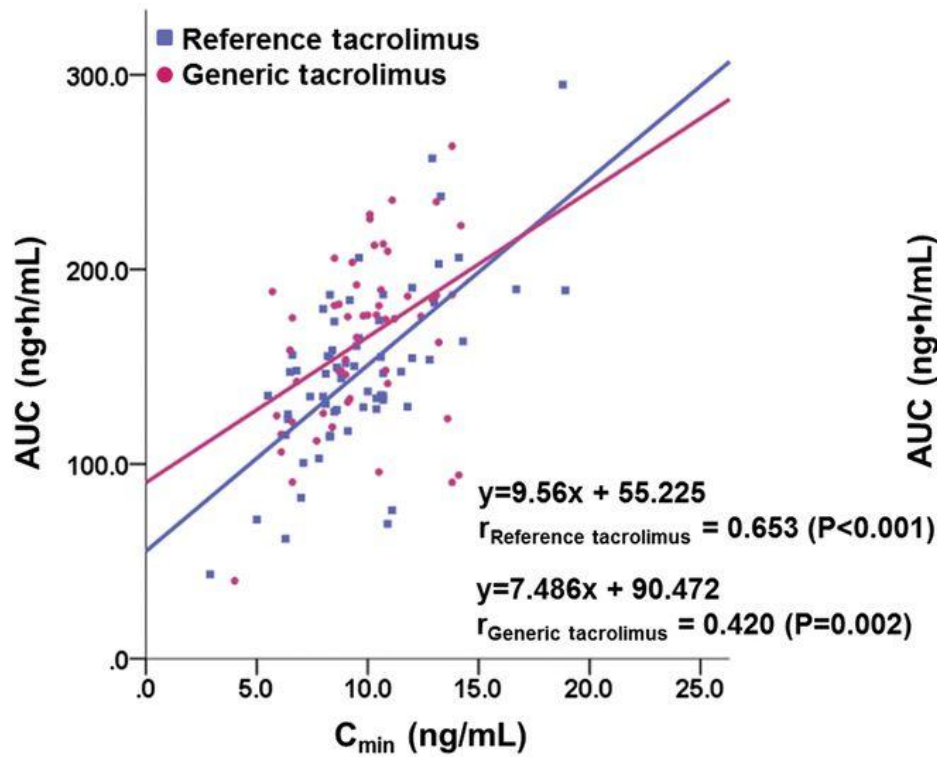
And what about 10% of patients that by definition are out of CI_{90} ?

Pharmacokinetic parameters on Day 10 (left panel) and at Month 6 (right panel) (de novo KTR).



	Day 10			Month 6		
	Reference (n=63)	Generic (n=54)	P-value	Reference (n=55)	Generic (n=38)	P-value
C_0 (ng/mL)	9.7±3.0	9.8±2.5	0.803	6.89±2.2	5.65±1.6	0.004
C_{max} (ng/mL)	23.4±9.1	35.1±14.5	<0.001	19.6±7.4	19.6±9.5	0.989
T_{max} (h)	1.4±0.8	1.0±0.5	0.002	1.54±1.11	1.31±0.87	0.309
AUC_{0-12} (ng.h/mL)	147.9±43.8	164.0±44.4	0.051	118.5±34.2	106.8±34.7	0.111
Dose/weight (mg/Kg)	0.13±0.05	0.14±0.08	0.447	0.086±0.04	0.069±0.03	0.040
Dose normalized C_0 (ng/mL/mg/Kg)	85.1±44.3	95.8±62.7	0.290	102.6±62.5	100.6±51.1	0.870
Dose normalized C_{max} (ng/mL/mg/Kg)	192.5±95.2	309.1±191.9	<0.001	273.2±148.9	346.3±184.4	0.056
Dose normalized AUC_{0-12} (ng.h/mL/mg/Kg)	1262.5±593.5	1513.4±935.4	0.084	1718.1±946.3	1882.2±935.6	0.429

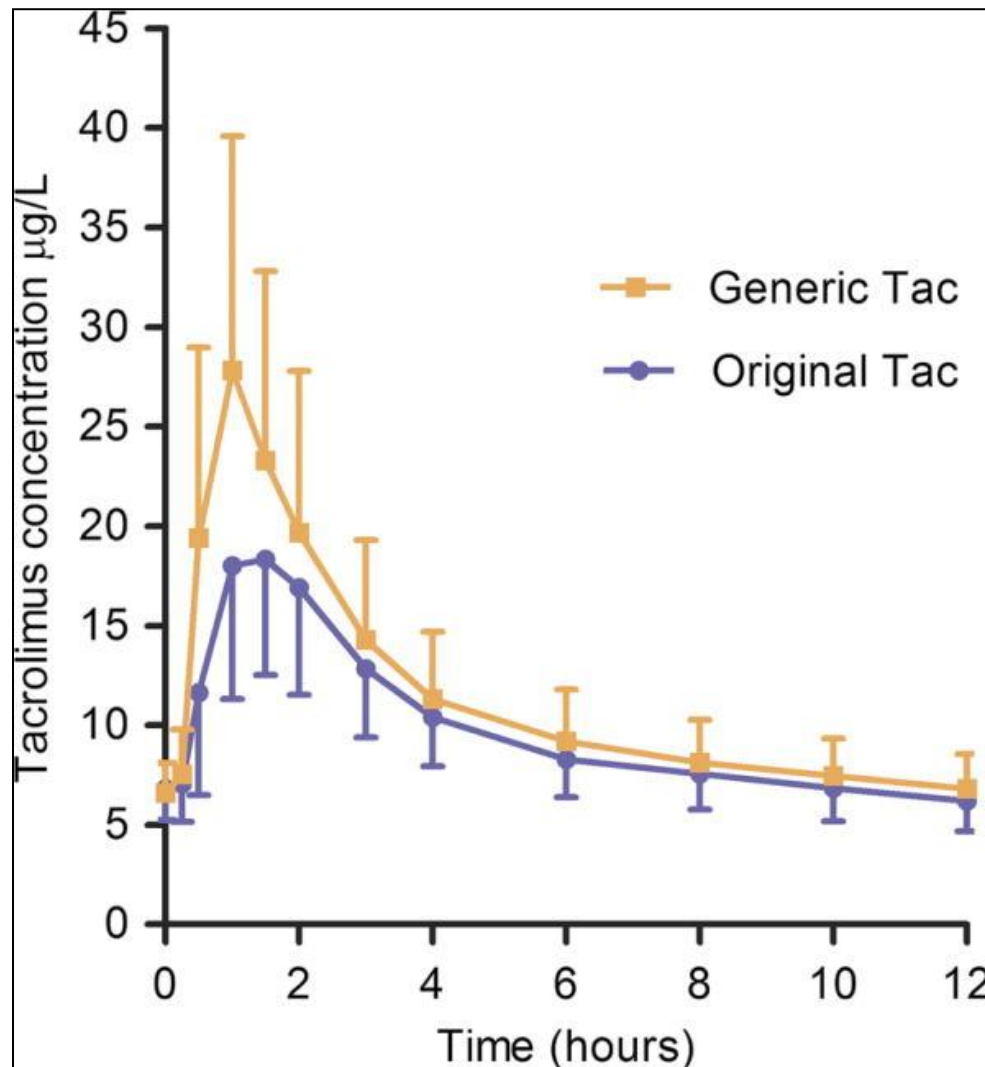
Correlation between C_{min} and AUC_{0–12} for reference tacrolimus and generic tacrolimus on Day 10 (left panel) and Month 6 (right panel).



Use of Generic Tacrolimus in Elderly Renal Transplant Recipients

Precaution Is Needed

Ida Robertsen,¹ Anders Åsberg,^{1,2} Aleksander Olsen Ingerø,¹ Nils Tore Vetthe,³ Sara Bremer,⁴ Stein Bergan,^{1,3} and Karsten Midtvedt²



No bioequivalence criteria

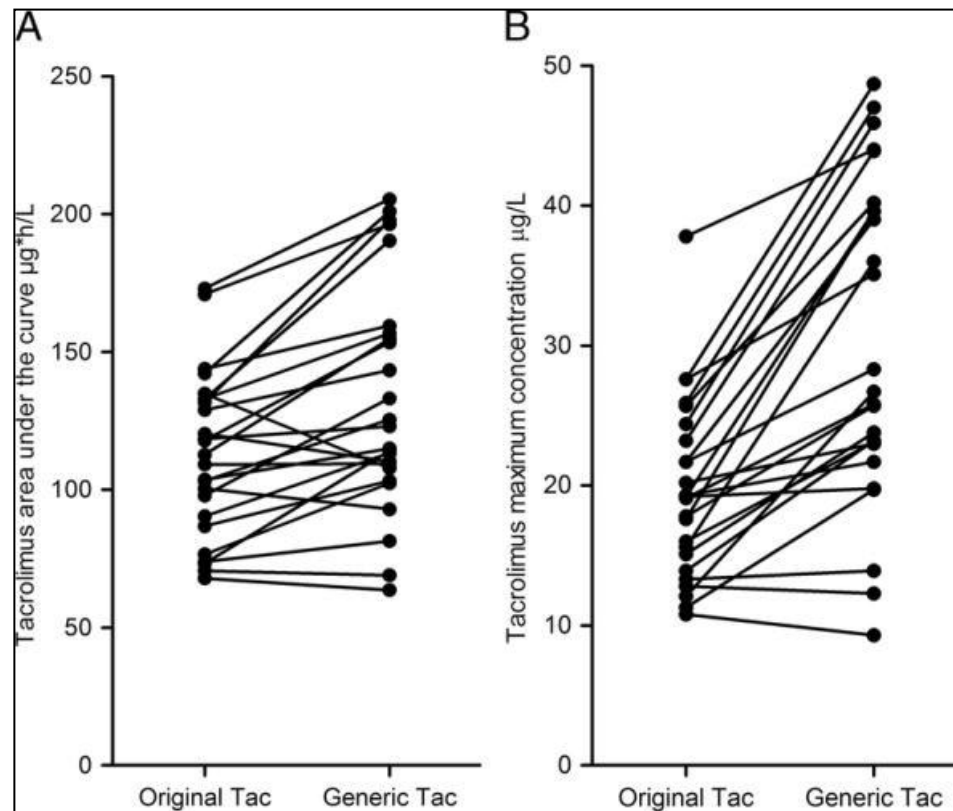
AUC ratio: 1.17 (CI₉₀ 1.1-1.23)

C_{max} ratio: 1.49 (CI₉₀ 1.35-1.65)

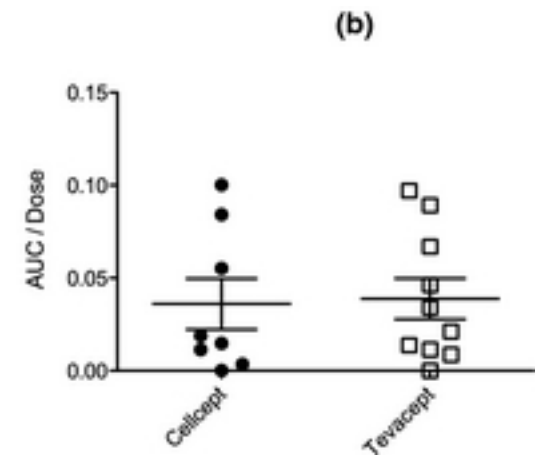
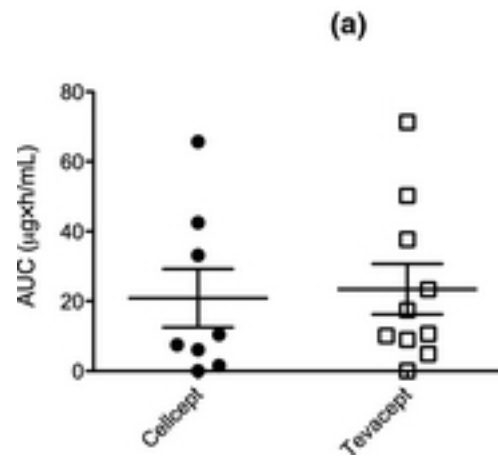
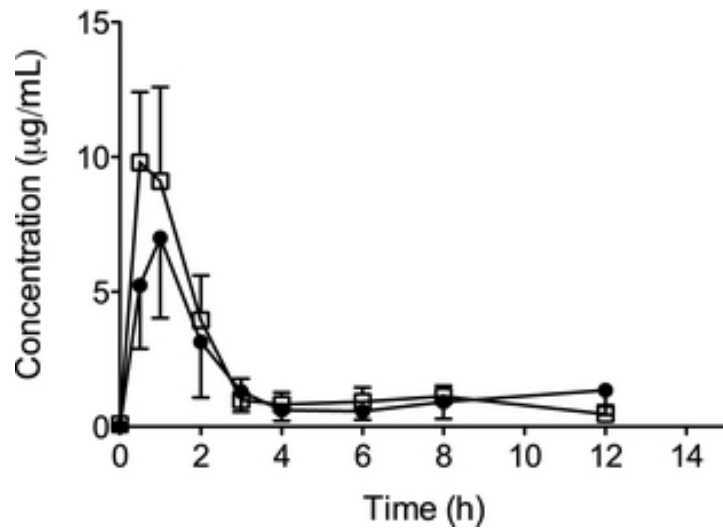
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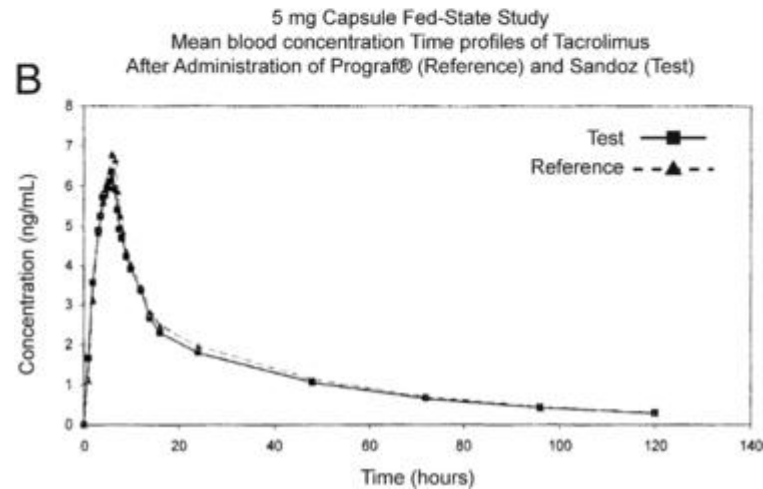
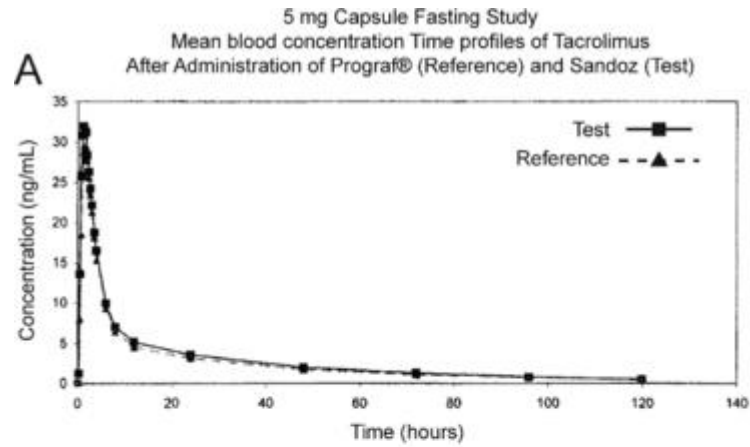
Ida Robertsen,¹ Anders Åsberg,^{1,2} Aleksander Olsen Ingerø,¹ Nils Tore Vetthe,³ Sara Bremer,⁴ Stein Bergan,^{1,3} and Karsten Midtvedt²



Bioavailability of a generic of the immunosuppressive agent mycophenolate mofetil in paediatric patients (ESRD in PD)



The “generic” effect of food on tacrolimus pharmacokinetics



Generic Immunosuppressants

- Bioequivalence in transplant recipients (not only HV)
- Patients subgroups (paediatric, black race, elderly...)
- Intra-patient variability greater in patients than HV
- Steady state
- Bioequivalence also based on clinical TDD (i.e. C_0)
- Generic prescription by transplant physicians
- Prescription “non substitutable”
- Avoid pharmacist switches
- Close follow-up
- Patient information (compliance)

Collateral effects (not damages) of generics

- Changes in pharmaceutical industry?
- Sub specialization?
 - Innovation
 - Development
 - Commercialization
- Wise prospection by pharmaceutical industry
- Drug hierarchy
- Innovation vs. cost/effectivity
- Drug development eras....

Collateral effects....

- Generics as comparators for cost/effectivity or cost/utility
- Comparator generics derived from innovator drugs developed 2 decades ago
- Risk of stagnation?